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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	
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07/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/823,259	KIENER ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-7,10,12-16,19 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-7,10,12-16,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/18/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date: _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 6/5/07, is acknowledged.

2. Claims 1, 5-7, 10, 12-16 and 18-20 are pending and under consideration as they read on a method of treating a hypoproliferative cell disorder or disorder involving increased cell death in a patient comprising administering to an EPHA2 antagonistic agent, wherein the antagonistic agent is an antibody.

3. Applicant's IDS, filed 6/5/07, is acknowledged.

4. In view of the amendment filed on 6/5/07, only the following rejections are remained.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 5-7, 10, 12-16 and 18-20 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action mailed 12/6/06.

Further, regarding anti-EphA2 antibody claimed in amended claim 12, the examiner directs application's attention to Carles-Kinch et al (cancer Res. 62:2847-2847, 2002, IDS C38) who teaches two types of EphA2 antibodies EA antibodies (EphA2 activating antibodies) and EN (antibodies that do not stimulate EphA2). Carles-Kinch et al evaluated the antibodies for their ability to inhibit tumor cell growth in soft agar or tubular network formation on matrigel (see table 1). Carles-Kinch et al teaches that EN1 and EN2 recognized different epitopes on EphA2 than those that were recognized by the different EA family (see page 2845, 1st col., 1st ¶). Carles-Kinch et al called EN antibodies as biologically neutral antibodies (See page 2844, 1st col., last ¶). Indicating that the ability of determining whether the antibody is EA or EN must be determined empirically. The specification fails to teach any anti-EphA2 antibody antagonist, EphA2 inhibitory antibodies. Accordingly, the disclosure is insufficient to enable the skilled artisan to make and/or use the claimed EphA2 antagonistic antibodies without undue and/or unreasonable experimentation. Carles-Kinch et al evaluated the effect of the EN antibodies on EphA2 activation and degradation, soft agar inhibition and tubular network formation inhibition, the EN antibodies were neutral. No antagonistic antibodies were found that decrease EphA2 phosphorylation, , gene expression or translation.

Applicant's arguments, filed 6/5/07, have been fully considered, but have not been found convincing.

Applicant contends that Pandey et al do not apply to the scenario in encompassed by the embodiments of the present invention relate to hypoproliferative cells, in other words, cells that do not grow and divide in a timely fashion to properly function in an organism. Applicant submits that Pandey does not apply to the scenarios contemplated by the present invention for the following reasons. The authors of the reference clearly focus on the migration of cells and do not comment on the proliferation, growth and survival of cells, features contemplated by the present invention. Also, the entire system studied by the authors does not reflect the cellular environment consisting of hypoproliferative cells described within the present specification. The experimental model consists of situations wherein transplanted cellular material is induced into an angiogenic state by external agents such as TNF-alpha and bFGF. In fact, some of the experiments within the article actually demonstrate that in the absence of these exogenous triggers, the explanted cellular material remains dormant (See Fig 2, page 567 and Fig 4, page 568) further discounting the usefulness of this reference in the context of the contemplated invention.

Contrary to Applicant's assertions Pandey et al teach that angiogenesis encompasses elements of endothelial cell proliferation [**on which B61 has no influence**] (emphasis added) and migration (see page 567, 3rd col., 1st ¶ in particular). Further, claim 7 requires that the use of the EphA2 antagonistic agent decreases EphA2 cytoplasmic tail phosphorylation relative. Pandey et al teach that anti-B61antibodies (anti-EphrinA1) of claim 13, which decrease EphA2 autophosporylation as claimed in claim 7, when administered to the rat corneas has no effect on vascularization in the cornea. It is the Examiner position that the identical chemical structure cannot have mutual exclusive functions. The properties Pandey et al discloses are necessarily present in the anti-EphrinA1 antibodies, that is no effect on vascularization in the corneas, including cell proliferation in the absence of evidence to the contrary.

Applicant submits that Rosenberg teaches that B61 (Ephrin-A1) stimulation of Eck(EphA2) results in increased proliferation, enhanced barrier function and enhanced restitution of injured epithelial monolayers using the human colonic adenocarcinorna derived CaCo-2 cells as a model for human intestinal epithelium. Applicants submit that Rosenberg does not apply to the scenarios contemplated by the present invention for a number of reasons. The reference teaches the CaCo-2 cell model of epithelial remodeling and only provides a single figure demonstrating Eck and B61 expression in cancerous and normal human tissue (Fig 1). The authors use this evidence as support for the conclusions derived from all the other experiments performed in the study. Moreover, the authors readily admit that although the addition of B61 increased the growth rates of selected cancer cell lines including the CaCo-2 cells in the study, the addition of B61 had no effect on the growth rate of normal melanocytes and that B61 has been reported to have no effect on the mitogenesis of cultured endothelial cells (pg G831, col 1 para 1). Furthermore, the data in Figure 7 discloses that at lower concentrations of B61 (0.01 gg/ml), no growth stimulation is observed. It is only at higher and arguably less physiological concentrations (0.1 ug/ml and 1.0 ug/ml) that mitogenesis is observed. The authors further disclose that the adenocarcinoma derived CaCo-2 cell line will spontaneously differentiate two weeks after reaching confluence, suggesting that these cells retain additional abnormal cell cycle regulatory mechanisms (page G826, col. 1, para 3). Applicant submits that the statements

discussed above, being directed to *hyper*proliferative cancer cells, clearly emphasize the differences of the studies disclosed in Rosenberg as compared to the therapeutic approach of targeting hypoproliferative cells with EphA2 antagonists to induce growth, proliferation and survival as encompassed by the present invention (emphasis added by Applicant).

However, as noted by Applicant Rosenberg teaches that the addition of B61 had no effect on the growth rate of normal melanocytes and that B61 (Ephrin A1) has been reported to have no effect on the mitogenesis of cultured endothelial cells (hypoproliferative cells compared to cancer cells). Given that EphrinA1 has no effect on the mitogenesis of cultured endothelial cells, it is unclear how the antagonistic agent such as anti-EphrinA1 antibodies would induce proliferation, growth, or survival of a hyporoliferative cell such as epithelial cells and endothelial cells.

Applicant points to Brantley-Sieders et al for support that EphA2 plays a role in angiogenesis and endothelial cell survival in vivo.

Contrary to Applicant assertion Brantley-Sieders et al reference teaches the role of EphA2 in endothelial migration induced by ephrin and vascular assembly. Brantley-Sieders et al do not teach the effect of EphA2 on endothelial cell proliferation, growth or survival.

Applicant points to the experiment depicted in Figure 8 (pg. 2047) demonstrates that EphA2 deficient endothelial cells are lost due to accelerated apoptosis when incubated in vivo. In fact, the authors also clearly state that "EphA2-deficient cells display decreased survival" (pg. 2045 col. 2, 1st para.) and "EphA2 RTK is also required for endothelial cell survival in vivo" (pg. 2045 col. 1, 2nd para.).

However, Brantley-Sieders et al teach that consistent with previous data, endothelial cell proliferation and apoptosis/survival in culture was not affected in the absence of EphA2 receptor (see page 2040, 1st col., line 1-3). Further, Brantley-Sieders et al teach that loss of the EphA2 receptor does not affect endothelial cell proliferation in vivo, however, EphA2 RTK is required for endothelial cell survival in vivo (see page 2045, 1st col.,). Brantley-Sieders et al do not address the issue at hand that is the use of EphA2 antagonistic agent such as antibodies result in induce cell proliferation, growth, or survival of a hypoproliferative cell. Brantley-Sieders et al do not demonstrate that EphA2 antagonistic agent would induce the survival of those EphA2-defecient endothelial cells. On the contrary, Brantley-Sieders et al teach that EphA2-deficient mice display impaired angiogenesis in response to ephrin-A1 stimulation in vivo (i.e., irresponsive to stimulation). Since EphA2-deficient mice do not express the EphA2, would not be responsive to EphA2 antagonistic agents too. Accordingly, an anti-ephrin-A1 antibody would not restore the survival of the EphA2-deficient endothelial cells. Applicant has not address the issue at hand, and Brantley-Sieders et al is considered irrelevant to the claimed invention.

Complete predictability of success of experimentation is not required under the law. Although the Examiner has provided publications that attempt to refute the predictability of the clinical value of the methods of the invention, based on the arguments above, Applicants submit that the various scenarios presented do not apply to the present invention. Pandey does not disparage and

may support the rationale for antagonizing EphA2 function to induce growth and survival of hypoproliferative cells. The CaCo-2 model presented in Rosenberg does not apply to the present invention due to the hyperproliferative nature of the cell line as well as the aberrant regulation of differentiation. Moreover, Applicants submit that Brantley-Sieders clearly supports the role of EphA2 in angiogenesis and endothelial cell survival in an in vivo model, presenting a far more compelling argument in support of the present invention.

However, since Applicant has not provided working examples and evidence to show that an EphA2 antagonistic agent such as antibody to EphrinA 1 would induce proliferation, growth, or survival of a hypoproliferative cell. Pandey is the closest art related to EphA2 antagonist, anti-EphrinA1 antibody, as in the claimed invention. Pandey uses the claimed antagonistic anti-EphrinA1 antibody with endothelial cells, and show that the antibody has no effect on vascularization in the cornea. In the absence of evidence to the contrary, Pandey is the controlling art for the enablement issue because it is the closest art to the invention.

Regarding the "an EphA2 antagonistic agent, wherein said agent is an antibody or an antigen binding fragment thereof", Applicant argues that it would have been merely routine experimentation to assay antagonist candidates for the effects described in the specification. Applicants respectfully submit that the specification clearly provides an enabling disclosure of what the functional limitations of the claims EphA2 antagonists would entail, and how to identify those antagonists.

However, Applicant has not provided sufficient biochemical information that distinctly identifies such "EphA2 antagonist" such as antibodies. While any antagonist to EphA2, such as antibodies may have some notion of the activity of the "inhibitory agent", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents, commensurate in scope with the claimed invention. The specification fails to provide any guidance on how to make any antagonist of EphA2, any antibody that can be used to induce proliferation, growth or survival of a hypoproliferative cell.

Therefore, one skilled in the art at the time of the invention would not be able to predict which EphA2 antagonist such as antibodies will induce proliferation, growth or survival of a hypoproliferative cell. Consequently the skilled artisan would not know how to use the instant invention as broadly claimed. While experimental testing techniques using cell surface receptor binding compounds are available, it is not routine in the art to use such methods when the expectation of success is unpredictable based on the instant disclosure. Thus, it would require an undue amount of experimentation of one skilled in the art to practice the invention as broadly claimed.

The specification contemplated that anti-EphA2 agonist agents can be used to treat cancer (hyperproliferative disorder) while anti-EphA2 antagonist agents can treat hypoproliferative disorders. No such agents such as anti-Ephrin A1 antibodies were produced or tested, it is unclear if these assay results are predictive of decrease EphA2-endogenous ligand binding, upregulate EphA2 gene expression and/or translation, increases EphA2 protein stability or

protein accumulation, decrease EphA2 cytoplasmic tail phosphorylation, promote EphA2 kinase activity, increase proliferation of EphA2 expression cells, increase survival of EphA2 expression cell, and/or maintain/reconstitute the integrity of an epithelial and/or endothelial cell layer.

7. Claims 1, 5-7, 10, 12-16 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 12/6/06.

Applicant's arguments, filed 6/5/07, have been fully considered, but have not been found convincing.

Applicant submits that due to the well characterized properties of the EphA2 (Eck) antigen coupled with the advanced nature of the antibody art, Applicants assert that they are entitled to claims encompassing antagonistic EphA2 antibodies and methods of use thereof. EphA2 (Eck) was first sequenced and cloned in 1990 and as part of the study, antibodies were generated by immunizing rabbits with recombinant Eck (Lindberg et al. 1990, Mol. Cell. Biol. 10:6316-24). Many subsequent studies have utilized methods for generating antibodies against EphA2 including, for example, U.S. Patent No 6,927,203 (hereinafter "the '203 patent"). The '203 patent discloses the generation of at least 450 hybridomas specific for EphA2, of which the first four studied identified two distinct epitopes. Another study established a group of at least 44 hybridomas generated to the extracellular domain of EphA2 (Carles-Kinch et al. Cancer Research (2002) 62, 2840-2847), further demonstrating the well studied properties of the EphA2 antigen. Further, Applicants submit that given the well characterized nature of the EphA2 epitope, the specification clearly demonstrates that the Applicants were in possession of the claimed antibodies. Specifically, sections 5.2.1 and 5.2.1.1 describe antibody antagonists of EphA2, sections 5.2.1.2 and 5.2.3.1 describe methods of making and polynucleotides encoding antibody antagonists of EphA2, section 5.5 describe how to identify suitable antibody antagonists of EphA2 as well as section 5.6 which describes the therapeutic utility of antibody antagonists of EphA2. Applicants maintain that the specification is replete with teachings that provide ample guidance to the ordinary artisan to generate, identify and utilize antibody antagonists to the well characterized antigen, EphA2.

However, neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (EphA2 antagonistic antibodies) to describe the claimed genus, nor does it provide a description of structural features that are common to species (EphA2 antagonistic antibodies). The specification provides no structural description of EphA2 antagonist other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed EphA2 antagonist looks like. The specification's disclosure is inadequate to describe the claimed genus of EphA2 antagonistic antibodies.

The broad brush discussion of making and identifying EphA2 antagonist antibodies in the specification does not constitute a disclosure of a representative number of members. No such antagonist antibodies were made or shown to have activity. The specification's general discussion of making and identifying for antagonist antibodies constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed EphA2 antagonistic antibodies.

There is no described or art-recognized correlation or relationship between the structure of the invention, the EphA2 antagonistic antibodies and it's induction of proliferation, growth or survival function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of EphA2 antagonistic antibodies which retain the features essential to the instant invention.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

July 17, 2007

Maher Haddad

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